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Original research

Survival associated with the use of sentinel lymph node in addition to lymphadenectomy in early-stage cervical cancer treated with surgery alone: A sub-analysis of the Surveillance in Cervical CANcer (SCCAN) collaborative study

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ABSTRACT

Aim: The aim of this study was to assess whether the use of sentinel lymph node (SLN) in addition to lymphadenectomy was associated with survival benefit in patients with early-stage cervical cancer.

Methods: International, multicenter, retrospective study. Inclusion criteria: cervical cancer treated between 01/2007 and 12/2016 by surgery only; squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, FIGO 2009 stage IB1-IIA2, negative surgical margins, and laparotomy approach. Patients undergoing neo-adjuvant and/or adjuvant treatment and/or with positive para-aortic lymph nodes, were excluded. Women with positive pelvic nodes who refused adjuvant treatment, were included. Lymph node assessment was performed by SLN (with ultrastaging protocol) plus pelvic lymphadenectomy ('SLN' group) or pelvic lymphadenectomy alone ('non-SLN' group).

Results: 1083 patients were included: 300 (27.7 %) in SLN and 783 (72.3 %) in non-SLN group. 77 (7.1 %) patients had recurrence (N = 11, 3.7 % SLN versus N = 66, 8.4 % non-SLN, p = 0.005) and 34 (3.1 %) (N = 4, 1.3 % SLN versus N = 30, 3.8 % non-SLN, p = 0.033) died. SLN group had better 5-year disease-free survival (DFS) (96.0 %,95 %CI:93.5–98.5 versus 92.0 %,95 %CI:90.0–94.0; p = 0.024). No 5-year overall survival (OS) difference was shown (98.4 %,95 %CI:96.8–99.9 versus 96.8 %,95 %CI:95.4–98.2; p = 0.160). SLN biopsy and lower stage were independent factors associated with improved DFS (HR:0.505,95 %CI:0.266–0.959, p = 0.037 and HR:2.703,95 %CI:1.389–5.261, p = 0.003, respectively). Incidence of pelvic central recurrences was higher in the non-SLN group (1.7 % versus 4.5 %, p = 0.039).

Conclusion: Adding SLN biopsy to pelvic lymphadenectomy was associated with lower recurrence and death rate and improved 5-year DFS. This might be explained by the lower rate of missed nodal metastasis thanks to the use of SLN ultrastaging. SLN biopsy should be recommended in patients with early-stage cervical cancer.

Introduction

Cervical cancer remains a major burden being the fourth most common cancer diagnosed worldwide [1]. Radical hysterectomy with sentinel lymph node (SLN) biopsy and/or pelvic lymphadenectomy is the standard treatment for patients with apparent early-stage cervical cancer [2,3]. There is evidence for the high accuracy of SLN in detecting lymph node metastases and the reduced morbidity associated with SLN biopsy [4–7]. Nevertheless, the oncological safety of SLN alone is still investigational [8–10]. In this context, the use of SLN in addition to systematic pelvic lymphadenectomy has been promoted by international guidelines [11]. In fact, SLN with ultrastaging analysis could provide important information about the presence of low volume metastases, which have been demonstrated to be associated with worse oncologic outcomes [12,13]. Moreover, ultrastaging of SLN might represent a tool to avoid the missed detection of lymph node metastasis. Finally, intraoperative assessment of a limited number of lymph nodes is more feasible than frozen section of a full lymphadenectomy.

The aim of this study was to assess whether the use of SLN in addition to pelvic lymphadenectomy had an impact on 5-year disease-free survival (DFS) in patients with early-stage cervical cancer, from the cohort previously included in the SCCAN collaborative studies [14,15]. Secondary aims were 5-year overall survival (OS) and pattern of recurrence.

Materials and methods

The SCCAN was an international, multicenter, retrospective study [14,15]. The SCCAN study consortium consisted of 20 tertiary centers from Europe, Asia, North America or Latin America. Imaging modalities used in clinical staging included: magnetic resonance imaging (MRI), expert ultrasound, computed tomography (CT) or positron emission tomography/computed tomography (PET/CT). Surgery and pathology were performed by surgeon and pathologist with experience in gynecologic oncology, respectively, and institutional follow-up was performed by physicians (according to international guidelines).

Patients were included if they met the following inclusion criteria: histologically confirmed cervical cancer treated between January 2007 and December 2016; squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma; primary surgical management; FIGO 2009 stage IB1-IIA2 with or without positive pelvic nodes at histology who underwent radical hysterectomy or fertility sparing procedures (radical trachelectomy, simple trachelectomy and conization); all included patients had negative surgical margins. Only patients who underwent laparotomy were included in order to reduce the risk of bias associated with possible adverse effects of the minimal invasive approach [16].

Patients undergoing neo-adjuvant chemotherapy or radiotherapy, adjuvant treatment and those with positive para-aortic lymph nodes were excluded, in order to select only patients relevant to the primary outcome. Lymph node assessment could have been performed by SLN plus pelvic (with or without para-aortic) lymphadenectomy ('SLN' group) or pelvic (with or without para-aortic) lymphadenectomy alone ('non-SLN' group). All SLNs from patients included in this study were submitted for ultrastaging protocol. SLN ultrastaging protocols have been previously described in another sub-analysis of the SCCAN study [13]. Micro-metastases were defined as metastatic deposits between 0.2 and 2.0 mm and isolated tumor cells as cancer deposits no greater than 0.2 mm. Isolated tumor cells (ITCs) were considered as non-metastatic lymph nodes [12,13].

The protocol was approved by the institutional review board of the lead institution (General University Hospital in Prague, Czech Republic) in 2016. Institutional review board approval at the participating sites was a prerequisite for participation. The study was performed in accordance with the Declaration of Helsinki.

Statistical analysis

Demographics and clinical data were summarized using absolute counts and percentages. DFS was defined as the time interval between the date of surgery and the evidence of the first disease recurrence or death from disease. OS was defined as the time interval between the date of surgery and date of death from any cause. Both intervals were censored at the date of last follow-up if no event was observed. We used the Kaplan–Meier method to estimate the distribution of time-to event end points of DFS and OS and differences among curves were assessed by the log-rank-test [17,18]. Multivariable analysis was performed using the Cox proportional hazard model and Hazard Ratios (HR) were reported with their 95 % confidence intervals. Differences in patients' characteristics were evaluated with the Chi-square test while differences in pattern of recurrences were assessed using the Fisher exact test. Surgical volume per center was binarized according to the median number of the surgeries performed per each center in the entire study period.

Patients were divided into two groups: 'SLN' (including all patients undergoing SLN biopsy with systematic lymphadenectomy) and 'non-

SLN' (including patients undergoing systematic lymphadenectomy without SLN biopsy). Lymph node recurrence was calculated as pelvic lateral plus inguinal lymph node recurrence and reported as DFS events. Sensitivity, negative predictive value and accuracy were calculated using lymphadenectomy histology as reference standard. IBM SPSS statistical software v. 27.0 and R v. 4.1.2, library 'survival' and 'survminer' were used.

Results

Patients' characteristics

Starting from a database of 4343 patients, we selected 1083 (24.9 %) patients according to inclusion criteria (Figure 1). Of the included patients, 300 (27.7 %) underwent SLN mapping and pelvic lymphadenectomy (SLN group) and 783 (72.3 %) underwent pelvic lymphadenectomy alone (non-SLN group). Table 1 shows the clinical and pathological characteristics of the included patients. Most patients were diagnosed with FIGO 2009 stage IB1 (N = 990, 91.4 %), squamous cell carcinoma (n = 698, 64.5 %), grade 2 (N = 764, 70.5 %) and negative LVSI (N = 574, 53.0 %). Seven (0.9 %) and six (2.0 %) patients had metastatic lymph nodes at final pathology in the non-SLN and SLN group, respectively. These patients did not receive adjuvant therapy due to patients' refusal after consent. Baseline difference between the two study groups was found in age (younger in SLN group), type of surgical procedure (SLN performed more frequently in case of fertility sparing surgery), LVSI (higher number of positive LVSI in SLN group) and grade (more 3 in SLN group). No difference in the incidence of pelvic lymph node metastasis was noted (Table 1). SLN was performed more frequently in some centers compared to other centers ($p < 0.001$, Supplementary Table 1), and also there was a higher use of SLN in the second study period (24.3 % in 2007–2011 versus 32.5 % in 2012–2016, $p = 0.004$, Supplementary Table 2).

Tracer used to detect SLN was radiocolloid in 181 (60.3 %), blue dye in 283 (94.3 %) (combined radiocolloid and blue dye in 177 - 59.0 %), indocyanine green in 5 (1.7 %) and unknown in 8 (2.7 %) patients. Median number of SLN retrieved per patient was 3 (range, 1–7). Sensitivity, negative predictive value and accuracy of SLN were 100 % (95 % CI: 75.3–100), 100 % (95%CI: 98.7–100) and 100 % (95%CI: 98.7–100).

Survival analysis

The median follow-up time of the included patients was 61.2 months (IQR: 39.6–85.2). The 5-year DFS in the entire cohort was 93.1 % (95 % CI: 91.5–94.7) and 5-year OS was 97.1 % (95 %CI, 95.9–98.3). Seventy-seven (7.1 %) patients had recurrence (N = 11, 3.7 % in SLN versus N = 66, 8.4 % in non-SLN, $p = 0.005$) and 34 (3.1 %) patients died in the entire cohort (N = 4, 1.3 % in SLN versus N = 30, 3.8 % in non-SLN, $p = 0.033$). The SLN group had better 5-year DFS compared to the non-SLN group (SLN 96.0 %, 95 %CI: 93.5–98.5 versus non-SLN 92.0 %, 95 %CI: 90.0–94.0; $p = 0.024$) (Figure 2). No difference in 5-year OS was found (SLN 98.4 %, 95 %CI: 96.8–99.9 versus non-SLN 96.8 %, 95 %CI: 95.4–98.2; $p = 0.160$) (Figure 3). Performing SLN and lower FIGO stage were the only independent factors associated with improved DFS at multivariate analysis (HR 0.505, 95 %CI: 0.266–0.959, $p = 0.037$ and HR 2.703, 95 %CI: 1.389–5.261, $p = 0.003$, respectively) (Table 2). These results were confirmed after removing patients with lymph node metastasis (Supplementary Table 3). Pattern of recurrence is reported in Table 3. Lymph node recurrence was not different between the two groups (SLN N = 1 (0.3 %) versus non-SLN N = 7 (0.9 %), $p = 0.46$), while there was a higher incidence of pelvic central recurrences in lymphadenectomy alone group (SLN N = 5 (1.7 %) versus non-SLN N = 35 (4.5 %), $p = 0.039$).

Discussion

In this study we demonstrated that performing SLN biopsy in addition to pelvic lymphadenectomy was associated with better 5-year DFS when compared to the systematic lymphadenectomy alone, in patients with cervical cancer undergoing primary open surgery and no adjuvant therapy. The use of SLN and low pathological stage were the only independent factors associated with improved DFS. Lastly, higher incidence of pelvic central recurrences and deaths was found in the pelvic lymphadenectomy alone group.

Other series had previously analyzed the impact of SLN on survival. One study by Buda et al. showed that ultrastaging analysis increased the detection of low volume metastasis, but the type of nodal staging (SLN versus lymphadenectomy) did not have an impact on 3-year DFS [19]. Conversely, in the study by Berasaluce Gómez et al. [20] patients with negative lymph nodes and positive Sedlis criteria undergoing SLN and lymphadenectomy had an increased risk of death compared with those undergoing lymphadenectomy, yet with non-significant difference in relapse rate. A recent meta-analysis investigated the impact of SLN alone versus pelvic lymphadenectomy alone on survival for patients with early-stage cervical cancer and concluded that no DFS and OS difference was found between the two populations [21]. In our study, which

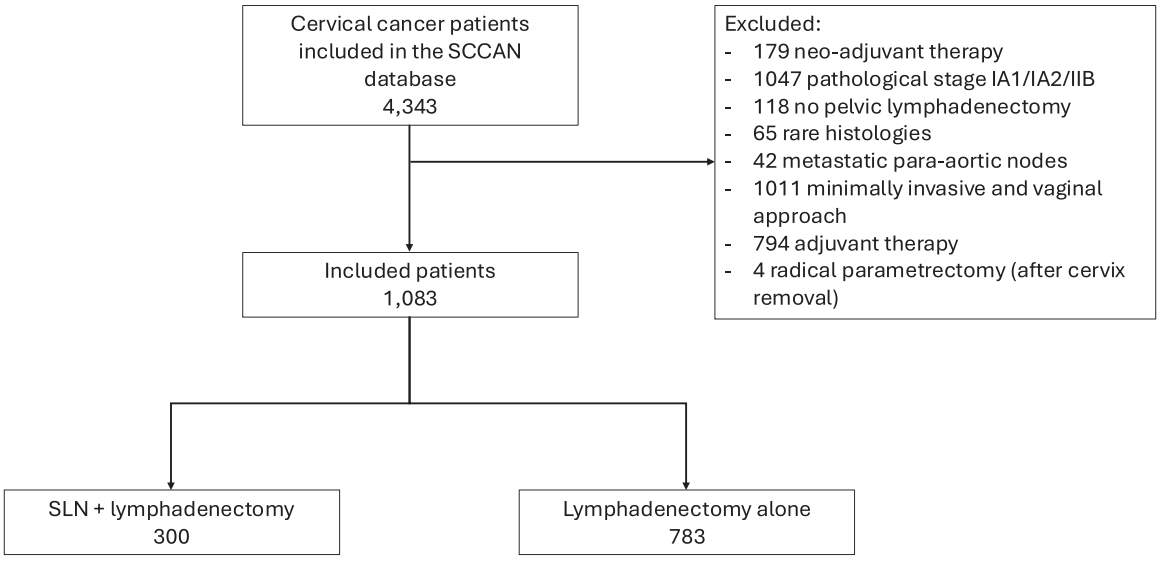

Fig. 1. Flow chart showing excluded and included patients.

Table 1
Distribution of demographical and clinical variables according to SLN.

	TOTAL (N = 1083)	Non-SLN (N = 783)	SLN (N = 300)	p-va
AGE (years)				**0.039**
≤ 45	627 (57.9)	438 (55.9)	189 (63.0)	
> 45	456 (42.1)	345 (44.1)	111 (37.0)	
PATHOLOGICAL TUMOR FIGO 2009 STAGE				0.991
IB1	990 (91.4)	715 (91.3)	275 (91.7)	
IB2	65 (6.0)	47 (6.0)	18 (6.0)	
IIA1	24 (2.2)	18 (2.3)	6 (2.0)	
IIA2	4 (0.4)	3 (0.4)	1 (0.3)	
SURGICAL PROCEDURE				< **0.001**
Conization	1 (0.1)	1 (0.1)	0	
Radical hysterectomy	1009 (93.2)	760 (97.1)	249 (83.0)	
Radical trachelectomy	60 (5.5)	12 (1.5)	48 (16.0)	
Simple hysterectomy	12 (1.1)	9 (1.1)	3 (1.0)	
Simple trachelectomy	1 (0.1)	1 (0.1)	0	
GRADE				< **0.001**[a]
1	114 (10.5)	71 (9.1)	43 (14.3)	
2	764 (70.5)	579 (73.9)	185 (61.7)	
3	205 (18.9)	133 (17.0)	72 (24.0)	
LVSI				< **0.001**[b]
No	574 (53.0)	472 (60.3)	102 (34.0)	
Yes	287 (26.5)	200 (25.5)	87 (29.0)	
Unknown	222 (20.5)	111 (14.2)	111 (37.0)	
HISTOLOGY				0.454
Squamous	698 (64.5)	511 (65.3)	187 (62.3)	
Adenocarcinoma	328 (30.3)	229 (29.2)	99 (33.0)	
Adenosquamous	57 (5.3)	43 (5.5)	14 (4.7)	
DIAMETER				0.371
≤ 20 mm	663 (61.2)	489 (62.5)	174 (58.0)	
21 −40 mm	352 (32.5)	245 (31.3)	107 (35.7)	
> 40 mm	68 (6.3)	49 (6.3)	19 (6.3)	
PELVIC LN STATUS[c]				0.207
Negative	1070 (98.8)	776 (99.1)	294 (98.0)	
Positive	13 (1.2)	7 (0.9)	6 (2.0)	
LARGEST TYPE OF METASTASIS IN LN				< **0.001**
ITC	6 (0.6)	0	6 (2.0)	
MIC	4 (0.4)	0	4 (1.3)	
MAC	9 (0.8)	7 (0.9)	2 (0.7)	

[a] Grade 1–2 versus grade 3 p-value: 0.009
[b] Calculated only on patients with known data
[c] ITCs considered as negative lymph nodes [12,13]

excluded all women that received adjuvant treatment, SLN group had better DFS compared to lymphadenectomy alone, and this was confirmed at multivariate analysis. The lack of difference in OS might be attributed to the low number of events (while the number of deaths was significantly higher in non-SLN group), or to the fact that when patients recurred regardless of the group they were salvaged by the treatment at the time of recurrence. The difference between the observed outcomes and those from previous studies [19,20] can be explained by the fact that we included only patients with no adjuvant therapy. We hypothesize that potential microscopic disease may have been missed by the lack of ultrastaging in the lymphadenectomy alone group. This may be an explanation for a higher incidence of recurrences. Of note, despite a higher proportion of women with low volume lymph node metastases

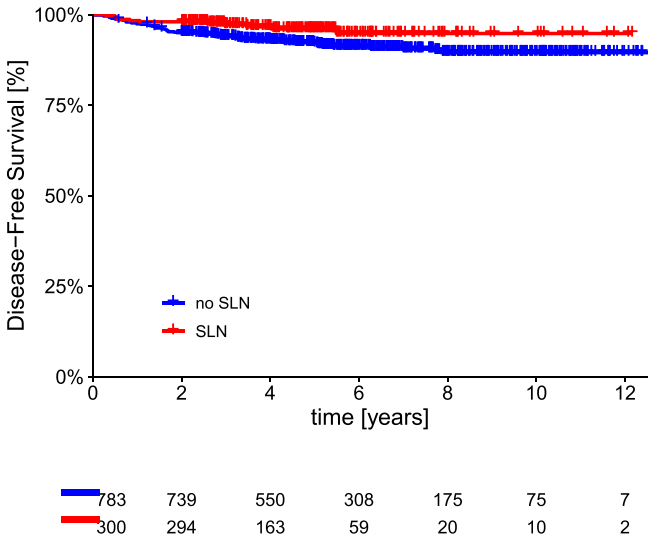

Fig. 2. Disease-free survival in patients undergoing lymphadenectomy and SLN biopsy versus non-SLN biopsy (p = 0.024).

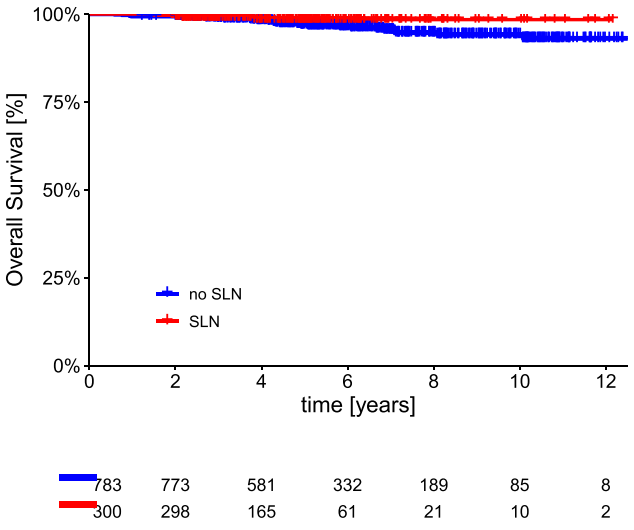

Fig. 3. Overall survival in patients undergoing lymphadenectomy and SLN biopsy versus non-SLN biopsy (p = 0.160).

(who refused adjuvant treatment), as well as other worse prognostic factors (LVSI and grade 3), a better prognosis was observed in the SLN group.

The poor prognostic role of micro-metastases in cervical cancer has been previously demonstrated [22], and a recent publication from the SCCAN consortium showed that the presence of nodal metastases ≥ 0.4 mm was associated with a significant negative impact on DFS and no cut-off value for the size of metastasis with better prognosis than node positive was found [13]. The more frequent identification of low volume metastases in the SLN group can be attributed to the use of ultrastaging analysis and has been previously described [19,23]. One might hypothesize that if ultrastaging was not done in the SLN group, all micro-metastases and isolated tumor cells, and probably some macro-metastases would be missed.

In this study, we found a different pattern of recurrence between the two study groups: higher incidence of central pelvic recurrences in the lymphadenectomy alone group. One could also expect a higher number of lymph node recurrences in this group (assuming the higher incidence of overlooked low-volume node metastases with consequent missed

Table 2
Cox univariate and multivariate analysis for risk of recurrence.

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	HR (95 %CI)	p-value	HR (95 %CI)	p-value
AGE (years)				
≤ 45	Ref.	**0.040**	Ref.	0.065
> 45	1.597 (1.021 −2.499)		1.526 (0.974 −2.390)	
PATHOLOGICAL TUMOR				
FIGO 2009 STAGE		**0.003**		**0.003**
IB1-IIA1	Ref.		Ref.	
IB2-IIA2	2.754 (1.415 −5.361)		2.703 (1.389 −5.261)	
FERTILITY SPARING SURGERY				
No	Ref.	0.835		
Yes	0.899 (0.328 −2.458)			
GRADE				
1 −2	Ref.	0.145		
3	1.365 (0.898 −2.075)			
LVSI				
No	Ref.	0.100		
Yes	1.500 (0.925 −2.432)			
HISTOLOGY				
Squamous	Ref.	0.315		
Adenocarcinoma	1.086 (0.663 −1.779)			
Adenosquamous	1.952 (0.881 −4.326)			
PELVIC LN STATUS				
Negative	0.433 (0.048 −93.49)	0.433		
Positive	Ref.			
SLN performed				
Non-SLN	Ref.	**0.027**	Ref.	**0.037**
SLN	0.486 (0.256 −0.922)		0.505 (0.266 −0.959)	
Surgical volume in the study period				
≤ 29	Ref.	0.113		
> 29	0.662 (0.398 −1.102)			

Table 3
Pattern of recurrence in the two study groups[d].

	Total (n = 1083)	No SLN (n = 783)	SLN (n = 300)	P value
Pelvic central	40 (3.7)	35 (4.5)	5 (1.7)	**0.039**
Lymph node	8 (0.7)	7 (0.9)	1 (0.3)	0.46
Abdominal liver	6 (0.6)	4 (0.5)	2 (0.7)	0.67
Abdominal other	11 (1.0)	10 (1.3)	1 (0.3)	0.31
Thorax lungs	14 (1.3)	11 (1.4)	3 (1.0)	0.77
Thorax other	1 (0.1)	0	1 (0.3)	0.28
Bones	2 (0.2)	1 (0.1)	1 (0.3)	0.48
Brain	1 (0.1)	0	1 (0.3)	0.28
Ovary	1 (0.1)	1 (0.1)	0	0.99
Other distant	2 (0.2)	1 (0.1)	1 (0.3)	0.48

[d] One patient might have had multiple recurrence sites at the same time.

opportunity for adjuvant therapy in the non-SLN group), but this was not significantly different. These results might be explained by the low incidence of nodal recurrences (N = 8, 0.7 %) and the higher incidence of central pelvic recurrence (N = 40, 3.7 % - representing most of relapses in our study). Interestingly, 7/8 (87.5 %) nodal recurrences were observed in the non-SLN group, thus supporting the theory of potential miss of lymph node metastasis in absence of ultrastaging. Moreover, patients in the non-SLN group might have had higher incidence of central pelvic recurrence since, if they had SLN, the lymph node metastases would have been detected and adjuvant therapy administered. In fact, exclusion of patients who underwent adjuvant therapy left patients treated by surgery only in whom missing a nodal metastasis due to the lack of ultrastaging resulted in a higher risk of recurrence. Therefore, we might postulate that node-negative patients in the SLN group are real negative as at least one lymph node was ultrastaged, while node-negative patients in the lymphadenectomy group might have had metastases overlooked by the pathologist with consequent higher incidence of central pelvic recurrence (low volume in-transit cancer cells left behind in the pelvis and not radiated caused pelvic recurrence).

With this study we also showed that, despite ICG (more recently demonstrated to be the tracer associated with highest rate of bilateral SLN mapping [24]) was used only in 1.7 % of patients (patients were included when SLN biopsy technique was under development), we achieved optimal results in terms of sensitivity/accuracy (100 %).

Strengths of the present study include the fact that it involved patients from 20 international referral centers, with the perioperative management following national and international guidelines. The study has limitations: firstly, the retrospective nature. No information was available regarding the selection of SLN versus lymphadenectomy for each patient. We did not report information on depth of stromal infiltration and on regimens used for treatment of recurrences and for documentation of recurrent disease (imaging alone, on biopsy proven histology, or both). There was a difference in SLN use across different centers as well as a potential historical bias. Lastly, lack of central pathology review and different ultrastaging protocols might represent a potential issue when comparing SLN outcomes.

Conclusion

Adding SLN biopsy to pelvic lymphadenectomy was associated with improved 5-year DFS, lower death rate and lower rate of central pelvic recurrences in patients with cervical cancer undergoing primary surgery and no adjuvant therapy. The use of SLN and a low pathological stage were the only independent factors associated with improved DFS. Association of SLN with improved survival might be explained by the reduced number of missed nodal metastases thanks to the use of the SLN ultrastaging protocol. SLN biopsy should be recommended in patients with early-stage cervical cancer even if lymph node dissection is performed.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Abu-Rustum received research funding paid to the institution from GRAIL. Memorial Sloan Kettering Cancer Center also has equity in GRAIL. All remaining authors have declared no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114310.

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